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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/431,594	11/01/1999	JEFFERY J. WHEELER	16303-002430	8936

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 12/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/431,594	WHEELER ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42 and 44-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42 and 44-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-29-03 has been entered.

2. The rejection of claim 62 under 35 USC 102(e) is withdrawn in view of the new grounds for rejection set forth below.

Response to Amendment

3. The Semple Declaration under 37 CFR 1.132 filed 9-29-03 is insufficient to overcome the rejection of claims 42 and 44-61 and 63-75 based 35 USC 102(e) as anticipated by Choi et al. as set forth in the last Office action because: the declaration fails to set forth the facts regarding the particular novel physical characteristics of Applicant's nucleic acid: lipid particles that are associated with the method of preparation of said nucleic acid:lipid particles disclosed in the specification as filed.

The Semple Declaration argues that loading/encapsulation methods disclosed in Choi et al. are not useful for loading nucleic acids into liposomes because nucleic acids do not readily cross intact lipid membranes. However, it is frst noted that the instant claims *do not recite* that the nucleic acid in the nucleic acid:lipid particles of the invention are *entrapped* inside a lipid particle. The Semple Declaration provides an opinion that the methods of Choi et al. would not produce nucleic acid: lipid particles wherein said nucleic acid is resistant in aqueous solution to degradation with a nuclease. The opinions of the Semple Declaration are not supported by

experimental evidence. According to Semple one would not expect to see any entrapment of the plasmid DNA in the liposomes, because the state-of the-art during 1994-1995 was to prepare cationic liposomes and, then to complex the preformed cationic liposomes with DNA in an aqueouse solution to form DNA-cationic liposome complexes. Moreover, Semple states that given that DNA does not readily cross lipid membranes and that the cationic lipids present in the external membrane of vesicles would electrostatically interact with the negatively charged DNA, the mixing of DNA with preformed cationic liposomes in an aqueous solution does not result in entrapment of DNA within the internal, aqueous space of liposomes. However, contrary to Semple's assessment of the Choi et al. reference, it is noted that Choi et al. specifically state that after the lipids of Choi et al. are prepared, these lipids may be utilized in the formation of liposome structures incorporating or entrapping one of more bioactive agents (see col. 13, lines 35-44). Moreover, the liposome formulations prepared in Example 9, provides evidence that the liposomes prepared according to the teachings of Choi et al. are capable of entrapping a bioactive agent. There is no evidence that the same methods of Choi et al. could not be used to entrap a bioactive agent, wherein said bioactive agent is a nucleic acid molecule.

Response to Arguments

4. Claims 42, 44-61 and 63-75 remain rejected under 35 U.S.C. 102(e) as being anticipated by Choi et al. for the reasons of record set forth in the Official Action mailed 5-16-02.

Applicant's arguments filed 9-29-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the prior art reference does not disclose each and every aspect of the claimed invention as amended. In particular, Applicants argue that the loading/encapuslation methods disclosed in Choi et al. are useful for

loading small molecules (e.g., vinca alkaloids, ets.) into liposomes, but are not useful for loading nucleic acids into liposomes because nucleic acids do not readily cross intact lipid membranes. However, contrary to Applicant's assertions, the Semple Declaration makes no mention of the influence of pH and temperature on the DNA permeability of the liposomes used in Example 9 of Choi et al. Absent evidence to the contrary, the conditions used in the preparation of the liposome/vincristine encapsulation method are useful in the preparation of nucleic acid: lipid particles.

Moreover, Applicant's argue that in contrast to the teachings of Choi et al., the novel methods by which nucleic acids are entrapped or encapsulated according to the present invention. However, it is again emphasized that the features upon which Applicant relies, namely the novel methods for entrapping nucleic acids, are not recited in the instantly claimed invention. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Additionally, Applicant's arguments do not comply with 37 CFR 1.111(c) because they do not clearly point out the patentable novelty which he or she thinks the claims present in view of the state of the art disclosed by the references cited or the objections made.

As stated in the prior Office Actions, Choi et al. teach liposomes for the delivery of bioactive agents comprising DODAC, DOPE and PEG-ceramide (col. 2, ln. 66, to col. 3, ln. 15; col. 24, ln. 15, to col. 26, ln. 25). Choi et al. teach conjugated lipids including PEG-ceramide or PEG-phosphatidylethanolamine, wherein the conjugated lipid inhibits aggregation of the particles. Choi et al. disclose liposomes having PEG-ceramide where the ceramide has 8, 14,

and 20 carbons (Table 11, for example). Choi et a1. teach that the PEG-conjugated lipids inhibit agregation of the hposomes (col. 24, lns. 26-32) and that the size of the liposomes ranges from 89-103 nm (col. 24, lns. 46-47). Choi et al. further disclose preparing the liposomes with 5% PEG-cexamide or 5% PEG-DSPE (col. 24, lns18-19), and with 10% PEG-ceramide (col. 26, lns. 2-3). Choi et al. specifically teach that the bioactive agent portion of the liposome may be nucleic acids including oligonucleotides intended to block production of some protein within the cell (col. 17, ln. 66, to col. 18, ln. 24).

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 42, 44-61, 63-64, and 67-75 are rejected under 35 U.S.C. 102(e) as being anticipated by Holland et al. (US Patent No. 5,885,613)

Holland et al. disclose fusogenic liposomes that can be used to deliver drugs, peptides, proteins, RNA, DNA or other bioactive molecules to the target cells of interest (col. 2, lines 12-43). Moreover, the liposomes may be used in the delivery of therapeutic genes or oligonucleotides intended to induce or to block production of some protein within the cell. The liposomes of Holland et al. comprise a lipid capable of adopting a non-lamellar phase, yet capable of assuming a bilayer structure in the presence of polyethyleneglycol-ceramide conjugate, wherein said lipid is a member selected from phosphatidylenthanolamines (including DOPE, see col. 4, lines 7-60) phosphatidylserines, ceramides, glycolipids and mixtures thereof; and a polyethyleneglycol-ceramide conjugate reversibly associated with said lipid to stabilize said lipid in a bilayer structure, wherein said polyethyleneglycol-ceramide conjugate is present at a concentration ranging from about 0.05 mole percent to about 50 mole percent. The liposomes of Holland et al. further comprise a cationic lipid, wherein said cationic lipid is selected from 3β-(N-(N',N'-dimethylaminoethane)carbamoyl)cholesterol, N,N-distearyl-N,N-dimethylammonium bromide, N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide, diheptadecylamidoglycyl-spermidine,N-(1-(2,3-dioleyloxy)propyl)-N-(2-(sperminecarboxamido) ethyl)- N, N-dimethyl ammonium trifluoroacetate, N-(1-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammoniumchloride,N-(1-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride and N,N-dioleyl-N,N-dimethylammonium chloride (see col. 7, line 55 to col. 8 line 67).

The liposomes of Holland et al. are preferably 0.05 microns to about 0.45 microns in size (col. 12, lines 11-13). Additionally, the fatty acid carbon chains of the PEG-ceramides may be saturated or unsaturated and have lengths ranging from C_2 to C_{31} (col. 9, lines 53-57).

Generally, the drugs loaded/encapsulated (col. 13, lines 24-42) into the liposomes of Holland et al. will be present in an amount from about 0.01 ng/mL to about 50 mg/mL. Furthermore, the liposomes of Holland et al. allow the encapsulated therapeutic agent to avoid the endocytic pathway, thereby the therapeutic agent would not be exposed to acidic conditions and/or degradative enzymes that could inactivate said therapeutic agent (col. 2, lines 30-43).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 62 is rejected under 35 U.S.C. §103(a) as being unpatentable over Choi et al.

Claim 62 recites the nucleic acid:lipid particle of claim 42, wherein said nucleic acid is a ribozyme. The discussion of Choi et al. as set forth above is incorporated here. However, Choi et al. does not specifically disclose nucleic acid: lipid particles, wherein said nucleic acid is a ribozyme.

Choi et al. specifically teach that the bioactive agent portion of the liposome may be nucleic acids including oligonucleotides intended to block production of some protein within the cell (col. 17, ln. 66, to col. 18, ln. 24). The genus of nucleic acid molecules well known in the art at the time the invention was made, that function in blocking the expression of a protein was so small, including for example: antisense oligonucleotides, antigene oligonucleotides such as triplex forming oligonucleotides, and ribozymes, that the artisan of ordinary skilled would at once envisage the claimed species. Therefore, disclosure the genus of oligonucleotides capable

of blocking expression of a protein encompasses ribozyme and antisense species (see MPEP 2 131.02). One of ordinary skill in the art at the time the invention was made, seeking to explore alternative nucleic acids capable of blocking protein expression, would have been motivated to substitute one well-known nucleic acid capable of blocking the expression of a gene for another, in this case a generic oligonucleotide with a ribozyme, with the expectation that the substitute nucleic acid molecule would function in an equivalent manner as the generic oligonucleotide, specifically by blocking the translation of mRNA into protein, thereby blocking protein expression.

Therefore, the invention as a whole would have been *prima facie* obvious over Choi et al. at the time the invention was made.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE